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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,674	06/30/2003	Gavin J. C. Braithwaite	42222-0011	5352

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,674	BRAITHWAITE ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-90* is/are pending in the application.

4a) Of the above claim(s) *81-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment of 3/7/06 amended claims 1-8, 10, 11, 13, 15-25, 27-29, 31-38, 41, 43, 44, 49-59, 66, 67, 70-77, 79 and 80.

Claims in the application are 1-90.

Claims 81-90 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/7/06.

The restriction requirement is traversed on the ground that the examiner has not demonstrated a serious burden needed to justify the restriction. While "serious burden" was not been explicitly recited, a serious burden is clearly apparent from the inventions of Groups I and III being unrelated as set forth in the restriction requirement, and inventions of Groups I and II being related but distinct since the article of the Group II invention can be produced by a process materially different from the process of the Group I invention. The restriction requirement is still considered proper, and is adhered to and made final.

Claims examined on the merits are 1-80

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support is not found in the specification for "polymeric sub-units" being alternative to monomers in claim 5, and for "collagen sub-units" in claim 7. The specification nowhere recites "polymeric sub-units" and "collagen sub-units".

Support is not found in the specification for the range of claim 8 having "1 nanometer" as a lower limit since the specification fails to recite "1 nanometer".

The specification does not recite a range with "(parallel)" as a lower limit in claim 11, and support for this range is not found.

The specification fails to recite "revolutions per second" in claim 13 to support this limitation.

In claim 27 and where recited in any other claim, the specification fails to recite "collagen sub-unit" to support this recitation.

In claim 35, the specification fails to recite "guiding or channeling" to support this recitation.

The specification fails to recite a range of "between 1 and 10 microns" in claim 41. Support is not found for a lower limit of 1 micron.

The specification fails to recite "further extracellular matrix", in claims 57, 71, 74 and 75, and support for the extracellular matrix being "further" is not found.

Claim Rejections - 35 USC § 112

Claims 3-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 3, the meaning and scope of "aligned polymer" and "textured polymer" is uncertain. Polymer characteristics that determine whether the polymer is aligned or textured are uncertain.

In claim 4 reciting "connective tissue, including a ligament, a tendon, a fascia and annulus fibrosis" makes unclear as to connective being required. The specific connective tissues should be required in a Markush group in a dependent claim further limiting the connective tissue of claim 4.

In claim 5, the difference in a monomer and "polymeric sub-unit" is uncertain, and it is uncertain as to the portion of the polymer that is a sub-unit. In line 7, only the monomers are aligned. What happened to the sub-units? In line 8, there is not antecedent basis for "the flow field". Additionally, "polymeric structures in the direction of the flow field" is unclear as to meaning. In line 11,

there is not clear antecedent basis for "the aligned polymers", and it is unclear how one would know when the polymers are aligned.

Claim 7 is unclear how claim 5 is further limited since there is not antecedent basis in claim 5 for "collagen sub-units", and other steps in claim 7. The method of claim 7 appears to be a complete method without depending on claim 5, and is a method that is a substitute for the method of claim 5. The claim should be an independent claim. Additionally, the meaning and scope of "collagen sub-units" is uncertain as to the portion of collagen that is a sub-unit. This also applies to claim 27.

Claim 11 is unclear as to degrees required by "(parallel)". Also, the purpose of putting parallel in parenthesis is uncertain. If parallel is zero degrees, zero degrees is not an angle.

Claim 16 does not have clear antecedent basis for "the structured layer".

Claim 23 does not have clear antecedent basis for "the preceding layer".

In claim 35, the difference in "guiding" and "channeling" required as alternatives is unclear.

Claim 43 does not have clear antecedent basis for "the wetting" (line 2).

Claim 50 does not have clear antecedent basis for "the collagen monomers" (line 3).

Claim 51 does not have clear antecedent basis for "the polymerized layer" (line 3).

In claims 57, 71, 74 and 75, "further extracellular matrix" is unclear as to what the matrix is "further" to.

Response to Arguments

While amendments have overcome claim indefiniteness, claims still lack clarity for reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 1-4, 57, 62, 63, 70, 71 and 76-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (5,962,325) in view of Bessea et al (AV on form 1449) for reasons in the previous office action of 12/7/05, and for reasons herein.

The claims are drawn to producing a templated extracellular matrix by providing a nanostructured artificial template, contacting the template with cells, and culturing the cells to produce a templated extracellular matrix.

Naughton et al disclose culturing stromal cells on a three-dimensional matrix (paragraph bridging cols 10 and 11) to from stromal tissue. During culturing, extracellular matrix protein including collagen is produced in the matrix (col 6, lines 10-21). The three-dimensional matrix can be coated with collagen (col 11, line 12). Cells cultured on the matrix can be chondrocytes, fibroblasts and/or cells capable or producing collagen type II and other collagen types, and proteoglycans which are typically produced in cartilaginous tissues (col 6, lines 15-20, and col 14, lines 20-50).

Bessea et al disclose producing ordered collagen matrices for three-dimensional cell culture. The ordered collagen matrices contain fibrillar organization close to that *in vivo*.

It would have been obvious to use as the three-dimensional matrix of Naughton et al, the ordered three-dimensional collagen matrix of Bessea et al to obtain property of the collagen matrix having a fibrillar organization close to that *in vivo*. The collagen matrix is inherently a nanostructured artificial template. After seeding and culturing stromal cells on the matrix as disclosed by Naughton et al, the matrix will be a templated extracellular matrix since extracellular matrix protein is produced by the stromal cells during culture as disclosed by Naughthon et al (col 6, lines 12-22). The matrix will inherently have a first and second surface as required by claim 58. Adding a growth factor as disclosed by Naughton et al (col 11, lines 39-42) will activate the cells as required by the last line of claim 1. The template being unstressed as in claim 70 and being subjected to tensile stress as in claim 71 would have inherently resulted when using a matrix for stromal cell culture as set forth above. For example, handling the matrix will result in tensile stress, and the matrix will be unstressed during culturing.

Response to Arguments

Applicants urge that there must be motivation or suggestion to make the proposed combination. However, Bessea et al disclose that the ordered collagen matrices contain fibrillar organization close to that *in vivo*. This fibrillar organization close that that *in vivo*

would have been motivation to use the three-dimensional collagen matrices of Bessea et al as the three-dimensional matrix of Naughton et al.

Applicants urge that Naughton et al do not produce a support structure as in the instant invention, which is highly ordered and resembles very closely the structure of the target connective tissue or stroma. However, the present claims do not require producing a structure more highly ordered and more closely resembling connective tissue than in Naughton et al. Moreover, the collagen matrices of Bessea et al contain fibrillar organization close to that *in vivo*, and would have resulted in a structure closely resembling connective tissue.

In response to arguments concerning Bessea et al, the claims do not require producing a structure that contains extracellular matrix more closely resembling a target extracellular matrix. The instant claims do not require a motion of fluid.

Claim Rejections - 35 USC § 103

Claims 58-61, 64, 65, 68, 69 and 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1-4, 57, 62, 63, 70, 71 and 76-80 above, and further in view of Vacanti et al (6,455,311 B1).

Claim 58 and claims dependent thereon require stacking a plurality of templated extracellular matrix layers to form a multilaminar templated extracellular matrix.

Vacanti et al disclose a laminar structure having multiple layers of tissue. The laminar structure is prepared by forming a mold or template, seeding and culturing cells on the mold or template to produce a tissue layer, removing the tissue layer, and assembling multiple tissue layers to obtain the laminar structure (col 5, lines 5-25, col 5, lines 25-43, paragraph bridging cols 12 and 13, and col 13, lines 15-30).

When producing stromal tissue on a matrix as disclosed by Naughton et al and using a collagen matrix as suggested by Bessea et al as set forth above, it would have been obvious to produce a laminar structure having multiple layers of tissue as suggested by Vacanti et al. Producing different layers having different cells as in claims 60 and 61 would have been suggested by Vacanti et al producing different tissue layers using different cells (paragraph bridging cols 12 and 13), and Naughton et al using a mixture of cells (col 14, lines 18-20). The template being unstressed as in claim 72, the matrix being subjected to tensile stress as in claim 73, and the matrix being unstressed as in claim 74 would have inherently resulted when producing and using a laminar structure as set forth above.

Response to Arguments

Applicants urge that Vacanti et al does not produce a target tissue that is highly ordered target tisse. However, the present claims require no step or condition that will produce a more highly ordered tissue than will be obtained when using the matrix of Bessea et al as the matrix of Naughton et al.

Claim Rejections - 35 USC § 103

Claims 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1-4, 57, 62, 63, 70, 71 and 76-80 above, and further in view of Lyons et al (AT3 on form 1449) or Nusgens et al (AX3).

The claims require activating mammalian fibroblasts by treatment with ascorbic acid, or ascorbate salts or esters.

Lyons et al disclose that adding ascorbate to culture medium for primary avian tendon cells stimulates procollagen gene transcription.

Nusgens et al disclose that in fibroblast cultures, vitamin C (ascorbic acid) stimulates collagen production.

When culturing fibroblasts as
the cells of Naughton et al and using a matrix as suggested by Bessea et al as set forth above, it would have been obvious to add ascorbate or ascorbic acid when culturing to stimulate collagen production as suggested by Lyons et al or Nusgens et al.

Response to Arguments

This rejection has not been separately traversed.

Claim Rejections - 35 USC § 103

Claims 5-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1-4, 57, 62, 63, 70, 71 and 76-80 above, and further in view of Ruberti et al (AS5).

Claim 5 and claims dependent thereon require controlling flow of a polymer solution into a device having a substrate and the device

generating shear flow to induce alignment of polymer structures to produce the nanostructured artificial template.

Ruberti et al disclose nanoscale engineering of type I collagen fibrils to mimic the multiple layers of aligned lamellae in cornea by polymerizing type I collagen on the surface of a rotating substrate under shear conditions to obtain aligned collagen fibrils.

When using a collagen matrix as suggested by Bessea et al as the matrix of Naughton et al as set forth above, it would have been obvious to produce the collagen matrix as taught by Ruberti et al to obtain aligned collagen fibrils. The conditions of claims depending on claim 5 would have been obvious from conditions disclosed by the references.

Parent application 10/306,825 does not antedate Ruberti et al since the present application is a continuation-in-part of the parent application, and the present invention is not disclosed in the parent application. Ruberti et al appears to have been published in 2003 prior to filing of the instant application, and the inventive entity of the present invention is different from the authorship of Ruberti et al since Melotti is an author and not an inventor. Therefore, Ruberti et al is a reference even through inventors Ruberti and Braithwaite are also authors.

Response to Arguments

This rejection has not been separately traversed.

Claim Rejections - 35 USC § 103

Claims 5-17 and 19-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1-4, 57, 62, 63, 70, 71 and 76-80 above, and further in view of Lee et al (WO 00/34442) (AN) and Agarwal et al (AS).

The claimed invention is described above.

Lee et al disclose applying shear flow stress to smooth muscle cells such that the cells align perpendicular to the direction of flow to produce implantable structures.

Agarwal et al disclose using shear flow to induce orientation during polymerization of rigid rod-like molecules.

When using a collagen matrix as suggested by Bessea et al as the matrix of Naughton et al as set forth above, it would have been obvious to produce the collagen matrix using shear flow to align collagen fibrils as suggested by Lee et al using shear flow to align cells and Agarwal et al using shear flow to align rigid rod-like molecules during polymerization. Since shear flow can align both the cells and the molecules, it would have been expected that shear flow will also align collagen fibrils which is desirable due to the fibrils being aligned *in vivo*. The conditions of dependent claims would have been obvious from conditions suggested by the references.

Response to Arguments

Applicants urge that Lee et al align cells. However, Agarwal et al align molecules that are rod-like, and it would have been expected

that shear flow will align collagen fibrils. The present claims do not require producing a thin highly aligned polymeric film.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David M. Naff
Primary Examiner
Art Unit 1651

DMN
6/9/06